

Impact case study (REF3b)

Institution: Newcastle University
Unit of Assessment: UoA4
Title of case study: Establishing effective doses of analgesics in animal research through a behaviour-based pain scoring system
<p>1. Summary of the impact</p> <p>Having recognised the relative under-use of analgesics (painkillers) in animal research and veterinary practice, a programme of research at Newcastle led to the development of a behaviour-based pain scoring system. This system provided an objective way of establishing effective doses of analgesics to reduce post-operative pain and discomfort in animals. This work led to changes to a range of policy statements, institutional policies (both academic and industrial) and individual research worker practices. It is now established that analgesics should be administered to rodents and rabbits, and that the efficacy of this treatment should be assessed objectively, in both the laboratory and in veterinary practice.</p>
<p>2. Underpinning research</p> <p><u>Key Newcastle researchers</u> (Where people left/joined the university in the period 1993-2013, years are given in brackets)</p> <p>PA Flecknell, Professor and Director; JV Roughan (1998 onwards), Research Associate/Senior Research Associate (1998-2006), then Staff Scientist; CA Richardson (2002 onwards), Residency in Laboratory Animal Science (2002-2012), then Research Fellow.</p> <p><u>Background</u></p> <p>Each year several million research and veterinary procedures are carried out worldwide on small rodents and rabbits, with around 500,000 procedures carried out in the UK alone. These can result in post-procedural pain and suffering. Aside from the important animal welfare issues, pain can influence research outcomes. Therefore, the elimination or control of pain within animal research represents both good science and good welfare. In the 1990s, the use of analgesia in animal research was incorporated into UK and EU legislation. However, it was recognised that these were only broad guidelines that were having little impact on the refinement of animal analgesic use (Flecknell, 1994, PMID: 7967460). Indeed, neither the UK nor EU legislation included practical recommendations for the assessment and alleviation of post-operative pain in animals.</p> <p><u>Research</u></p> <p>The relative under-use of analgesics (painkillers) following surgical procedures in animal research was confirmed by the Newcastle group via informal contact with research workers and regulators, by an email survey, and by a series of literature reviews [R1, R2]. The use of analgesics to prevent or alleviate pain in animals used in research was reported to be minimal, if given at all. It was determined that a poor ability to recognise pain and the subsequent uncertainties surrounding the use of pain relief were the main reasons for this [R1, R2]. Crucially, any analgesics used were administered at arbitrary doses, with no evidence of efficacy. This was established by the Newcastle-run surveys [R1, R2] and a survey of research establishments conducted by the RSPCA (www.rspca.org.uk).</p> <p>In the late 1990s, Flecknell and his team at Newcastle began researching means of objectively assessing post-procedural pain in animals and the intensity of that pain, in order to enable efficient pain relief to be given. They analysed the behaviours of rabbits and rodents following surgical and non-surgical procedures, and distinguished behaviours specific to pain sensation [R3, R4, R5, R6]. A pain scoring system was developed and used in subsequent studies to establish appropriate and effective doses of analgesics [R3, R4, R5, R6]. This behaviour-based pain scoring system was evaluated against a simple subjective approach commonly used in clinical practice and research settings [R6]. Volunteer observers with experience in animal husbandry and care, were asked to watch video clips and assess post-operative pain in rats given different amounts of pain relief, initially using a visual analogue (numerical) scale. They were then given 10 minutes training in</p>

behaviour scoring before being asked to assess video clips once more. The ability to differentiate between the rats according to the treatment received was found to be significantly greater when the behaviour-based scoring system was implemented (75% compared to 54%) [R6].

3. References to the research

(All authors are Newcastle researchers. Citation count from Scopus, July 2013)

- R1. Richardson CA, Flecknell PA. (2005) Anaesthesia and post-operative analgesia following experimental surgery in laparotomy rodents – are we making progress? *ATLA*, 33, 119-127. **Cited by 44** (Copy held and available on request)
- R2. Stokes EL, Flecknell PA, Richardson CA. (2009) Reported analgesic and anaesthetic administration to rodents undergoing experimental surgical procedures. *Laboratory Animals*, 43, 149-154. DOI: 10.1258/la.2008.008020 **Cited by 25**
- R3. Roughan JV, Flecknell PA. (2001) Behavioural effects of laparotomy and analgesic effects of ketoprofen and carprofen in rats. *Pain*, 90(1-2):65-74. DOI: org/10.1016/S0304-3959(00)00387-0 **Cited by 94**
- R4. Roughan JV, Flecknell PA. (2003). Evaluation of a short duration behaviour-based post-operative pain scoring system in rats. *European Journal of Pain*, 7:397-406. DOI: 10.1016/S1090-3801(02)00140-4 **Cited by 59**
- R5. Roughan JV, Flecknell PA. (2004) Behaviour-based assessment of the duration of laparotomy-induced abdominal pain and the analgesic effects of carprofen and buprenorphine in rats. *Behavioural Pharmacology*, 15(7):461-72. DOI: 10.1097/00008877-200411000-00002 **Cited by 46**
- R6. Roughan JV, Flecknell PA. (2006) Training in behaviour-based post-operative pain scoring in rats- An evaluation based on improved recognition of analgesic requirements. *Applied Animal Behaviour Science*, 96, 327-342. DOI: org/10.1016/j.applanim.2005.06.012 **Cited by 9**

Selected funding awards

- 2002-2005 *Analgesia and Pain Assessment in Laboratory Animals*. Medical Research Council - £181,057
- 2004-2006 *Assessing Animal Health and Welfare and Recognising Pain and Distress*. 3Rs Foundation (Switzerland) - £33,659
- 2003-2006 Pain Assessment. Pfizer Ltd. - £25,695

External recognition of impact and quality of research

2005 International Academy of Pain Management Pfizer Award; 2006 Prince Laurent Foundation Award for Research Contributing to Animal Welfare; 2006 Eurotox/HSI/P&G Animal Welfare Award; 2007 Ben Cohen Award, International Committee for Laboratory Animal Science; 2007 FELASA Award for Research Contributions to Laboratory Animal Welfare; 2008 Academy of Surgical Research Markowitz Award; 2009 CAAT/Charles River Excellence in Refinement Award; 2012 Charles River LASA Award for Contributions to Laboratory Animal Welfare.

4. Details of the impact

In the 1990s, it was commonplace to see statements such as '[the] rodents did not experience pain' or 'rodents and rabbits show no signs of pain and so require no analgesics' in scientific publications. However, the Newcastle research has had a significant impact in changing such attitudes. This has led to worldwide changes in a range of policy statements, practice guides, institutional policies (academic and industrial) and individual research worker practices, with guidance on the use of animal analgesics within the UK being enforced by the Home Office. These changes relate to which analgesics are given and the dosing of these products as well as the assessment of pain via behavioural observations. The change in practice has clear benefits for animal welfare; ensuring that animals used in research suffer the minimum of pain and distress, which, in turn, also benefits scientific research, since pain is otherwise an uncontrolled variable which can adversely affect study results.

The findings of the research at Newcastle were summarised and disseminated to a wider audience via a website, workshops, conferences, a text book, book chapters, review articles and a Dutch

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television documentary. The website was set up with the aim of ‘...providing practical guidance in recognising signs of health and good welfare and to help users of the site to become better able to identify signs of pain, distress and poor welfare in laboratory animals’ (www.ahwla.org.uk).

UK policy and practice

In the UK animal research which may cause pain, suffering, distress or lasting harm is regulated under the Animals (Scientific Procedures) Act 1986. In England, Scotland and Wales, this Act is implemented by the Home Office. According to their statistics there were around 15,000 personal licences in force in the UK at the end of 2012 [EV a, p.23] and 4.11 million scientific procedures were started, with just over 3 million of these carried out on rodents [EV a, p.12]. The Home Office is required by the Act to thoroughly assess every research project involving an animal before granting a research licence and it is clearly stated in the licence conditions that ‘*The licence holder must use analgesia or another appropriate method to ensure that the pain, suffering and distress caused by regulated procedures are kept to a minimum*’ (Home Office: *Draft guidance on the Operation of the Animals (Scientific Procedures) Act 1986*, updated Jan 2013, p.95). The Home Office also carry out regular inspections to ensure that all animal research is in accordance with licence conditions and, as testified by the Head of the Animals in Science Research Unit (ASRU) at the Home Office, their inspectors ‘...frequently make use of [the Newcastle findings] when evaluating research procedures in rodents that require assessment and alleviation of post-surgical pain’ [EV b]. In addition, ASRU ‘...frequently recommend research workers to refer to [the Newcastle findings] when formulating their post-operative care regimens’ and ‘...regularly facilitate direct contact between research workers and [the] group at Newcastle whenever specialist advice on analgesia is required’ [EV b]. In 2012, 1.16 million research animals required anaesthesia during a procedure [EV a]. Flecknell makes a conservative estimate, based on his experience in the UK that at least 70% of these would require post-operative analgesics.

The *UK Joint Working Group on Refinement* publish reports that provide practical guidance on setting up and operating effective protocols for assessing the welfare of animals used in research and testing. Their report published in 2011 cites Roughan and Flecknell (2001) when stressing the importance of observing animals’ behaviours in order to assess potential pain levels [EV c]. They specifically state that it is necessary to observe each individual animal post procedure ‘...for at least 5 min to ensure that [any potential pain related behaviours] are detected’ [EV c; citing R3, Section 3].

International policy and practice

In the 2011 *US National Research Council of the Academy of Science Report* (Institute for Laboratory Animal Research), the underpinning Newcastle research is referenced (R1, R4 & R5, Section 3) in conjunction with the statement that ‘...fundamental to the relief of pain in animals is the ability to recognize its clinical signs in specific species’ [EV d, p.120]. This report informed revisions to *Pain and Distress in Laboratory Animals* guidelines, produced by *The Animal Research Advisory Committee* [EV e], which now clearly state that ‘*Preemptive measures should be taken to minimize or prevent the development of pain and/or distress*’, and that analgesic agents ‘...can have a positive effect on the speed with which animals return to normal behavior’ [EV e, p.3; citing R3 & R4 from Section 3]. These guidelines form part of the *National Institutes of Health* (NIH) policy and thus must be adhered to by all who are funded by NIH. NIH funds research at over 2,500 institutions and is the largest single source of funding for medical research. Thus, NIH policies impact significantly on animal research worldwide.

UFAW (Universities Federation of Animal Welfare) is internationally recognised as having led the way in improving, and promoting high standards of animal welfare, and their *Handbook on the Care and Management of Laboratory and Other Research Animals* serves to inform and guide practice. Their most recent edition (2010) extensively cites the Newcastle research in relation to the assessment of pain and welfare. The behaviour-based assessment developed at Newcastle and their researcher training system is suggested as an aid for researchers to ‘...identify and score pain more accurately and reliably’ [EV f, p.86].

In 2008, the Australian National Health and Medical Research Council published their *Guidelines*

to Promote the Wellbeing of Animals used for Scientific Purposes and in a chapter concentrating on assessing, minimising and monitoring pain they cite the Newcastle work (R3 Section 3) when highlighting the importance of being aware that in many species ‘...signs of pain or distress may be transient and interspersed with normal behaviour’ [EV g, p.30].

Education and training

The work at Newcastle has led to a major change in practice across the world, not only through implementation of guidelines but also a widespread use of the resulting educational materials in training courses. The website *AHWLA (Assessing the Health and Welfare of Laboratory Animals)* was set up (with support from the *Swiss 3R Research Foundation*) to provide practical guidance in recognising signs of health and good welfare and to help users of the site to become better able to identify signs of pain, distress and poor welfare in laboratory animals (www.ahwla.org.uk). In the period January 2008- July 2013, the website had over 70,000 unique visitors, and 900 copies of the CD ‘*Pain Assessment in the Rat*’ have been distributed worldwide. The CD is recommended as an educational resource for behaviour-based pain scoring in the Australian Guidelines to Promote the Wellbeing of Animals used for Scientific Purposes [EV g]. A senior clinical veterinarian and associate director of the Laboratory Animal Resource Centre at the University of California, San Francisco has delivered training courses for veterinarians and scientists across America and Brazil [EV h]. He certifies that:

‘The training videos are directly valuable in helping students and veterinarians identify particular pain behaviors they can monitor in laboratory animals, as well as supporting and stimulating discussion of the ethical and regulatory commitment to seriously address laboratory animal pain management’ [EV h].

These materials have also been used in obligatory courses for biologists and veterinarians performing animal experiments, run by Animalfree Research in Switzerland [EV i], and in the Netherlands [EV j].

5. Sources to corroborate the impact

- EV a. Home Office Statistics of Scientific Procedures on Living Animals Great Britain 2012: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/212610/spanimals12.pdf
- EV b. Letter of support: Head of the Animals in Science Research Unit (ASRU), Home Office
- EV c. Hawkins et al (2011). A guide to defining and implementing protocols for the welfare assessment of laboratory animals: eleventh report of the BVAAWF/FRAME/RSPCA/ UFAW Joint Working Group on Refinement. *Laboratory Animals* 2011; 45: 1–13. DOI: 10.1258/la.2010.010031
- EV d. National Academy of Science Report 2011: Guide for the Care and Use of Laboratory Animals (Copy held at Newcastle)
- EV e. *The Animal Research Advisory Committee: Pain and Distress in Laboratory Animals Guidelines* (Revised Nov 2012). http://oacu.od.nih.gov/ARAC/documents/Pain_and_Distress.pdf
- EV f. Hubrecht & Kirkwood (2010). *The UFAW Handbook on the Care and Management of Laboratory and Other Research Animals*. Blackwell Publishing Ltd, UK. <http://books.google.co.uk/books?hl=en&lr=&id=Wjr9u1AAht4C&oi=fnd&pg=PA76&ots=OSkXSkHAZA&sig=NgJC33uv2RIGloREmTOnTHwe1VI#v=onepage&q=flecknell&f=false>
- EV g. Australian Government National Health and Medical Research Council: Guidelines to Promote the Wellbeing of Animals used for Scientific Purposes (2008). Pdf available at: <http://www.nhmrc.gov.au/guidelines/publications/ea18>
- EV h. Letter of support: Acting Associate Director of the Laboratory Animal Resource Centre at the University of California, San Francisco
- EV i. Letter of support: Scientific Advisor to Animalfree Research, Bern, Switzerland.
- EV j. Letter of support: Assistant Professor in Dept. of Animals in Science and Society, Utrecht University, The Netherlands.